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REVERSAL OF MYOCARDIAL FAILURE IN ENDOTOXIN SHOCK WITH INSULIN

Linda T. Archer, Beverly K. Beller, Jane K. Drake,

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University of Oklahoma Health Sciences Center
Departments of Physiology and Biophysics, Medicine, and Research Surgery
Oklahoma City, Oklahoma

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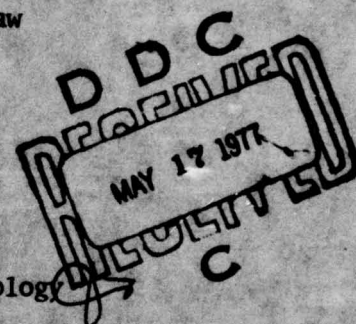
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ABSTRACT

Recent data reported from this laboratory have documented myo-
cardial dysfunction in canine endotoxin shock. The purpose of the
present study was to determine the separate effects of insulin and glu-
cose on the failing canine myocardium. Two groups of experiments were
conducted on isolated working left ventricular preparations in which
LD_{100} endotoxin was administered prior to, or following, isolation of
the heart. Myocardial dysfunction occurred between 2 and 6 hours post-
endotoxin, as evidenced by significantly increased left ventricular end
diastolic pressure, depressed power and negative dP/dt, although blood
glucose concentrations were maintained at control values. Insulin
infusion, at mean rates of 6 units/minute administered via left atrial
cannulation, reversed all signs of myocardial failure. During insulin
infusion, heart rates decreased ($p < 0.02$) and myocardial lactate uptake
increased ($p < 0.02$), while oxygen uptake and coronary blood flow were
insignificantly altered. Findings indicate that the positive inotropic
effects of insulin occur without additional oxygen requirements.

INTRODUCTION

Numerous studies have documented myocardial dysfunction in endo-
toxic or septic shock in man (Bell and Thal 1970; Cann et al. 1972;
Siegel et al. 1967), nonhuman primates (Cavanagh et al. 1970; Geocaris
et al. 1973; Greenfield et al. 1974) and dogs (Archer 1976; Hinshaw et
al. 1972, 1973a, 1974a, 1974b, 1976; Thal 1972). The precise mechanism
responsible for the failure in shock has not been substantiated although
inadequate coronary perfusion has been implicated as a significant deter-
minant (Greenfield et al. 1972; Hinshaw et al. 1974b) and substrate
deficiency has been suggested (Pindyck et al. 1974; Stremple et al. 1976;
Weisul et al. 1975). A direct toxic action of endotoxin on the myocardium
seems to have been excluded (Hinshaw et al. 1972, 1974a), and a proposed
adverse effect of a circulating myocardial depressant factor (Lefer 1970)
has not been confirmed (Hinshaw et al. 1974a).

Hypoglycemia has been cited as a causative factor in the patho-
genesis of endotoxin and septic shock in animals (Berk et al. 1970;
Filkins and Cornell 1974; Groves et al. 1974; Hinshaw et al. 1974c, 1975)
and man (Berk et al. 1970; Rackwitz et al. 1974; Yeung 1970). Hypo-
insulinemia has been reported in subhuman primate septic shock (Cryer
et al. 1971; Hinshaw et al. 1975) and in low output human septic shock
(Clowes et al. 1974). Diabetic-like glucose tolerance responses have
been observed in septic shock patients (Gump et al. 1974).

Recent reports have shown that glucose and insulin markedly improve
cardiac output in shock (Clowes et al. 1974; Pindyck et al. 1974; Stremple
et al. 1976; Weisul et al. 1975). Although the increases in cardiac output

and right and left ventricular stroke work observed in critically ill patients by Pindyck and associates (1974) were a result of intravenous administration of hypertonic glucose, infusions of 50% glucose did not prevent myocardial dysfunction when used in this laboratory (Hinshaw et al. 1976). Clowes et al. (1974) observed increases in cardiac output and mean arterial pressure with concomitant decreases in central venous and pulmonary wedge pressures in response to glucose, potassium and insulin administration. Ventricular performance was enhanced in the anoxic isolated perfused rat heart when treated with insulin, and it was concluded that insulin increased utilization of glucose (Weissler et al. 1973).

Majid and co-workers (1972) used a glucose-insulin-potassium (GIK) infusion in normal subjects as well as patients with severe ischemic heart failure. GIK increased cardiac output and left ventricular (LV) dP/dt, decreased left ventricular end diastolic pressure (LVEDP), and tended to decrease plasma potassium at both rest and exercise. Glucose alone did not affect any of the above parameters in normal subjects except for an increased left ventricular dP/dt at rest.

The purpose of the present study was to determine the separate effects of insulin and hypertonic glucose on the myocardium in endotoxin shock.

METHODS

Experiments were conducted on 13 isolated working canine heart preparations as previously described (Hinshaw et al. 1972, 1973a, 1974a, 1974b). Each study was composed of a large support dog (20-25 kg) providing arterial blood continuously for an isolated working heart with

ventilated lungs, obtained from a small adult donor animal (5-8 kg).
Coronary venous return was continuously obtained from a large-bore cannula
introduced into the right ventricle. The preparation was stabilized at a
mean arterial pressure of 100 mmHg and a cardiac output of 76 ml/min/kg
(based on the weight of the dog supplying the isolated heart). Intra-
ventricular pressures were monitored as previously described (Hinshaw
et al. 1972, 1973a, 1974a, 1974b). Cardiac inflow and blood temperature
were maintained constant. Mean aortic pressure was varied periodically
in order to evaluate the performance of the isolated heart in the steady
state. Under the conditions of these experiments, mean aortic pressure
equals mean orifice coronary pressure. Cardiac power (gm·meters/sec),
maximum positive (+) and negative (-) dP/dt (mmHg/sec) and myocardial
efficiency (%) were calculated as previously reported (Hinshaw et al.
1974a, 1974b). Coronary arterial and venous PO_2, PCO_2 and pH were measured
by an Instrumentation Laboratories blood gas analyzer, and arterial and
venous O_2 and CO_2 contents were determined by a Van Slyke manometric
apparatus. Arterial and venous blood glucose concentrations were deter-
mined with a Beckman glucose analyzer as previously reported (Hinshaw et al.
1976). A Chem 18 survey (Technicon Instrument Corp., Terrytown, N.Y.)
was used for potassium, calcium, sodium and chloride measurements.
Arterial insulin concentrations were determined by radioimmunoassay
(Phadebas insulin test, Pharmacia, Uppsala, Sweden) (Hinshaw et al. 1975).
Lactate determinations were carried out utilizing a procedure modified
after a published method (Hohorst 1965).

This laboratory has previously published data utilizing several iso-
lated working left ventricle preparations in which myocardial dysfunction
and failure can be documented and evaluated. These models include variable

periods of hypotension, plus the additional insult of endotoxin shock and injections of E. coli endotoxin administered before and after isolating the heart (Hinshaw et al. 1972, 1973a, 1974a, 1974b). A combination of two of the previously reported models was utilized (Hinshaw et al. 1972, 1973a, 1974a, 1974b). Although control experiments were not utilized in the present study, our recent report (Archer et al. 1975) clearly demonstrates the stability of the isolated working heart preparation. Experiments conducted for 6 hours on control, non-endotoxin-treated hearts documented stable values for LVEDP, myocardial efficiency, oxygen uptake, positive and negative dP/dt and coronary blood flow, while responsiveness to intermittent infusions of epinephrine was unaltered during the 6-hour period (Archer et al. 1975).

Studies were divided into two series, each having a distinct experimental purpose. In the first series, endotoxin was administered to the intact animals prior to transfer of the heart. The benefit of this preparation is that it allows a longer period of observation after endotoxin injection although individual controls were not conducted (Hinshaw et al. 1972, 1973a, 1974a). In the second series, experiments were conducted in which endotoxin was injected into the system after the heart was isolated and established in the perfusion circuit. The advantage of this preparation was that each heart served as its own control although time of observation from endotoxin injection was reduced (Hinshaw et al. 1974b). Hearts in the present study were subjected to low coronary pressures to exacerbate the dysfunction in the presence of endotoxin as previously documented (Hinshaw et al. 1974b), yet all performance, hemodynamic and metabolic parameters were compared only at identical mean aortic pressures.

Infusions of 50% glucose were used in both series in order to maintain blood glucose at control values. The procedure involved measuring blood glucose concentrations approximately every 20 minutes, and calculations for the amount of 50% glucose needed was based on blood glucose concentration and estimated blood volumes. Insulin was prepared at a concentration of 20 U/ml and infused at varying rates into the left atrium of the isolated heart. In Series 1 an injected bolus of 60 U followed by infused insulin was necessary due to the severe degree of heart failure. In both series the rate of infusion was initiated at 0.4 units/minute and an equilibration period of 3-5 minutes was allowed, then stepwise increments of insulin were infused. Mean values of insulin reported were the minimum amounts necessary to effect a recovery of steady-state myocardial performance to control (normal) values.

Series 1: Performance of Isolated Hearts Subjected to E. coli Endotoxin and 1.5 Hours of Aortic Hypotension (N=6); Endotoxin Administered to Intact Dog

E. coli endotoxin (LD_{90}), 2.5-3.0 mg/kg, was injected into both the heart donor dog and support animal 3-4 hours before isolating the left ventricle. Some degree of heart dysfunction was observed in five hearts (mean LVEDP, +9.0 mmHg) when the first performance and metabolic evaluations were made at a mean aortic pressure of 50 mmHg. Within 18 minutes after the initial evaluation period, mean LVEDP for all six hearts was +13.6 mmHg at 50 mmHg. In this series, 50% glucose infusions were begun approximately 20 minutes after the initial evaluation with only one heart receiving 50% glucose before this time. Therefore, heart dysfunction occurred although blood glucose concentrations remained or were maintained

at control values. Insulin was then infused into the left atria of the
isolated hearts. Initially, a bolus of insulin was injected (mean, 60 U)
and thereafter insulin was infused at a mean rate of 3 U/min until LVEDP
values were significantly decreased from the initial failing values.
After restored values for LVEDP were obtained with insulin infusion,
performance and metabolic characteristics of the heart were evaluated
at an aortic pressure of 50 mmHg. The average total amount of 50% glu-
cose necessary to maintain arterial glucose concentrations constant was
16 grams (32 ml).

*Series 2: Performance of Isolated Hearts Subjected to E. coli Endotoxin
and 3.5 Hours of Aortic Hypotension (N=7); Endotoxin Administered
in the Isolated State*

In these experiments an LD_{100} E. coli endotoxin (3.0 mg/kg) was
administered to both the isolated heart and support animal as previously
described (Hinshaw et al. 1974b). Each heart was sequentially evaluated
at mean aortic pressures of 150, 100 and 50 mmHg at control, 3.5
and 4.5 hours post-endotoxin, allowing 1-5 minutes at each pressure
for equilibration. Arterial and venous blood samples for determination
of O_2 and CO_2 content, glucose, insulin, potassium, lactate, PO_2, PCO_2
and pH values were drawn at a mean aortic pressure of 50 mmHg at control,
3.5 and 4.5 hours after endotoxin. Immediately after endotoxin injec-
tion, the heart was subjected to an average period of 3.5 hours of
aortic pressures between 25-50 mmHg. All blood samples were drawn at
50 mmHg and an adequate interval of time was allowed for performance and
hemodynamic parameters to reach a steady-state. Cardiac dysfunction or
failure was characterized by a statistically significant increase in
LVEDP (mmHg) and decreased power (g·m/sec). Approximately 90% of the

hearts failed in this series as was previously reported by this laboratory when this preparation was utilized (Hinshaw et al. 1974b). Although blood glucose had been maintained constant by 50% glucose infusion started approximately 1.5 hours after endotoxin, LVEDP values were significantly increased over control values at 3.5 hours post-endotoxin. Heart performance and metabolic parameters were evaluated again at 50 mmHg and arterial blood samples were drawn. After the documentation of heart dysfunction, insulin (Iletin, Eli Lilly & Co., Indianapolis, Indiana) was infused into the left atrium of the isolated heart. Each heart preparation was infused at a mean rate of 8 U/min, depending on the minimum amount of insulin needed to return myocardial performance characteristics to control values without increasing the heart rate. The third and final evaluation of heart performance and metabolism was made at 50 mmHg. The average total amount of 50% glucose necessary to maintain arterial glucose concentrations constant was 30 grams (60 ml).

RESULTS

Series 1: Effects of Insulin on Isolated Hearts Subjected to 1.5 Hours of Aortic Hypotension 5 Hours after Endotoxin (Glucose Concentration Maintained Constant)

Table 1 shows the effects of infusion with insulin on the performance and hemodynamic parameters for the six hearts in the first series. E. coli endotoxin (LD_{90}), 2.5-3.0 mg/kg, was administered to both the heart donor and support animal 3-4 hours prior to transfer of the heart and isolation of the left ventricle. The first performance curve was carried out in the isolated system 5 hours after endotoxin was administered to the heart donor dog. Data reveal that at the low aortic pressure of 50 mmHg, LVEDP was

+8.4 mmHg, although one of the six hearts did not exhibit dysfunction at this time. Within 18 minutes at 50 mmHg, LVEDP had increased to +13.6 mmHg, which served as further documentation of failure. Although arterial glucose concentration was normal at 97 mg%, the heart failure still occurred. At 6 hours post-endotoxin during insulin infusion, LVEDP values decreased to +5.4 ($p<0.005$) while power, stroke work, +dP/dt and -dP/dt were increased ($p<0.05$). Coronary flow and myocardial efficiency were unchanged although heart rate was significantly decreased ($p<0.02$).

Effects of insulin on arterial concentrations of potassium and lactate are shown in Table 2. It is seen that potassium levels significantly increase ($p<0.001$) while lactate remains relatively constant. Blood glucose concentration was maintained constant with infusions of 50% glucose.

The effects of treatment with insulin on the metabolic characteristics of hearts 5-6 hours after endotoxin are summarized in Table 3. O_2 uptake did not change during insulin treatment. CO_2 production, RQ and lactate uptake appeared to increase after insulin infusion, but these changes were not significant.

Table 4 summarizes the effects of insulin on performance characteristics in failing hearts with blood glucose concentrations maintained constant. LVEDP was decreased at 150 mmHg during insulin infusion ($p<0.05$) while +dP/dt increased at aortic pressures of 100 and 150 mmHg ($p<0.025$).

Series 2: Effects of Insulin and Glucose on Isolated Hearts Subjected to 3.5 Hours of Aortic Hypotension and Endotoxin

Results from seven experiments designed to evaluate myocardial performance and metabolism after a 3.5-hour period of aortic hypotension

and endotoxin with subsequent infusion of insulin are shown in Tables 5, 6 and 7.

Table 5 illustrates the effect of coronary (aortic) hypotension and endotoxin on the performance and hemodynamic characteristics of seven hearts. Significant increases in LVEDP (+3.6 to +6.1 mmHg, $p<0.01$), decreases in power (4.6 to 4.3 g·m/sec, $p<0.01$) and negative dP/dt ($p<0.05$) were observed 3.5 hours after endotoxin. Findings from Table 5 reveal that myocardial failure is prominent after endotoxin although hearts had been treated with 50% glucose for an average of 2 hours (mean arterial glucose concentration, 113 mg%). Although +dP/dt was not decreased, a complicating factor in the interpretation of changes in +dP/dt is that elevations in LVEDP in dysfunctioning hearts augment myocardial contractility which masks any observable diminished intrinsic contractility due to endotoxin (Hinshaw et al. 1974b).

The onset of insulin infusion into the left atrium was approximately 4 hours post-endotoxin. Results reveal that an infusion rate of 8 U/min corrected the myocardial failure since LVEDP and power returned to control values. Positive dP/dt increased above control values from 1357 to 1536 mmHg/sec ($p<0.05$) in spite of the lowered LVEDP values. Of particular interest is the marked increase in -dP/dt from -1482 to -1757 mmHg/sec ($p<0.02$) and decreases in heart rate ($p=0.02$) following insulin infusion.

Table 6 summarizes the effect of insulin on arterial concentrations of potassium and lactate while maintaining constant glucose levels with 50% glucose infusion. Potassium increased from 3.2 to 4.0 mEq/L ($p<0.001$) after endotoxin administration but was returned to control values after insulin. Lactate concentrations increased after endotoxin ($p=0.05$), indicating the severity of the shock state (Spitzer et al. 1974).

Table 7 shows the effect of hypotension, endotoxin and subsequent insulin infusion on myocardial metabolism. O_2 uptake remains unchanged throughout the experimental course, while CO_2 production and RQ were increased ($p < 0.02$) 3.5 hours post-endotoxin. During insulin infusion myocardial lactate uptake increased ($p < 0.02$) at 4.5 hours post-endotoxin.

The effects of insulin on performance and hemodynamic values at higher aortic pressures (100-150 mmHg) after hypotension and endotoxin are shown in Table 8. During insulin infusion, LVEDP (6.1 mmHg) and power (14.1 g·m/sec) were unchanged from control values of 6.4 mmHg and 14.2 g·m/sec, respectively, at 150 mmHg, demonstrating that insulin had reversed the failure previously demonstrated at lower aortic pressures (Table 5). There was a significant increase in +dP/dt ($p < 0.05$) and decrease in heart rate ($p < 0.05$) with insulin infusion.

DISCUSSION

The purpose of the present study was to determine the separate effects of insulin and hypertonic glucose on the failing myocardium after endotoxin and hypotension. Cardiac dysfunction was observed in the first series at 3.5 hours post-endotoxin as evidenced by increases in LVEDP and decreases in power. In the second series, LVEDP was significantly elevated at 5 hours post-endotoxin. Insulin infusions reversed the heart failures since LVEDP was decreased ($p < 0.02$) in both series to values

normally observed at 50 mmHg (Archer et al. 1975; Hinshaw et al. 1973b). Power was returned to control values in the first series and was significantly increased (p<0.01) in the second series.

Recently, Weisul and associates (1975) confirmed the presence of severe myocardial dysfunction in patients in low cardiac output septic shock and found that although isoproterenol therapy modestly improved performance, it did not correct the depression of cardiac function. On the other hand, a solution of GIK dramatically improved performance and corrected myocardial abnormalities; i.e., pulmonary wedge pressure was decreased from 14.6 to 10.1 mmHg (p<0.05), and left ventricular stroke work index increased from 9.46 to 45.3 g m/beats/m^2 (p<0.01) while heart rate was constant (Weisul et al. 1975). The unchanging heart rate reveals that the effect of GIK therapy used by Weisul's group was inotropic. These data corroborate the results of the present study since heart rates decreased from control during insulin infusion, suggesting a direct insulin action and not one derived from catecholamine release from the support animal. Currently conducted isolated heart studies reveal an increase in heart rate from 158 to 169 beats/min (p<0.005) at low doses of glucagon infusion (1 µg/min), and, since heart rates were unchanged after insulin in the present study, glucagon as an impurity in the insulin solution does not appear to be the agent mediating improvement of myocardial performance.

The majority of drugs with positive inotropic activity used in the treatment of heart failure produces an increased demand of oxygen by the myocardium (Majid et al. 1972) in spite of a lowered end diastolic pressure. However, in the present study, oxygen uptake did not increase with insulin infusion, suggesting that myocardial performance is enhanced

without additional oxidative requirements. Hypoinsulinemia has been documented in patients in low output septic shock (Clowes et al. 1974). Clowes equated the continued progression of myocardial insufficiency with further depression of insulin secretion, forming a vicious positive feedback circle. They further suggested that restoration of blood insulin levels by GIK demonstrated effectively the return of cardiovascular function in which a high cardiac output could be maintained to promote survival (Clowes et al. 1974). Hiatt et al. (1971) found that massive doses of insulin (2400 to 7500 units) prolonged survival in dogs for 30 hours to 10 days after ligation of the left circumflex artery, whereas control dogs treated with either saline or glucagon died within 16 minutes.

Clowes and associates (1974) were not able to explain the mechanism by which cardiac function was improved by GIK in septic shock, but suggested that glucose transport and glycolysis were enhanced and that the cell membrane potential was restored. Weissler and co-authors (1973) described the beneficial effects of insulin on the performance of the hypoxic isolated perfused rat heart and ascribed its benefit to increased myocardial utilization of glucose. The action of GIK solution in septic patients was suggested to be prevention of both potassium loss and sodium gain in myocardial tissue, thus supporting the transmembrane action potential and myocardial contractility (Weisul et al. 1975). In the present study the strong inotropic influence of insulin may have been mediated via the restoration of intracellular potassium into the myocardial cell. In both groups insulin infusion caused a significant decrease in arterial plasma potassium concentration, suggesting the possibility of restored cell membrane potential, thus positively affecting myocardial contractility.

Previous studies from this laboratory (Hinshaw et al. 1974b, 1976) have documented a depression of peak negative (-dP/dt) in endotoxin-treated heart preparations. It was previously speculated that depressed -dP/dt suggested an impairment of early ventricular relaxation, possibly interfering with diastolic filling (Hinshaw et al. 1974b). In the present study -dP/dt values were decreased 3-5 hours post-endotoxin. Grossman and McLaurin (1976) used the measurement of peak -dP/dt as an index of relaxation and have found decreased peak -dP/dt values in patients with myocardial ischemia compared with normal patients. They reported that myocardial relaxation may be impaired in the acutely ischemic ventricle and that altered elasticity of its wall caused stiffness of the ventricular chamber. Myocardial ultrastructural evaluations of the failing myocardium in endotoxin shock have revealed marked cardiac edema and accumulation of fluid between myofibrillar elements and within the mitochondria (Coalson et al. 1972). Whether the diminished -dP/dt results from defects in ionic mechanisms, a depression of elastic recoil forces, fluid accumulation between myofibrillar elements or other elements is unknown, but in both of the present series insulin infusion clearly increased -dP/dt, suggesting an improved ventricular function during diastole.

Lactate uptake increased significantly with insulin infusion in the present study, and this finding parallels previous work done by Spitzer and associates (1974) showing that arterial lactate concentration rises and lactate removal by the myocardium increases in endotoxic shock. These data also corroborate findings showing an increase in respiratory quotient (RQ) as a result of a shift from fatty acid to lactate utilization (Spitzer et al. 1974). Since the accuracy of our glucose method was ±3 mg/100 ml, increased glucose uptake by the myocardium in response to insulin could not be determined.

Hypoglycemia has been documented to perform a significant role in the pathogenesis of endotoxic and septic shock in animals (Berk et al. 1970; Filkins and Cornell 1974; Groves et al. 1974; Hinshaw et al. 1974c, 1975) and man (Berk et al. 1970; Rackwitz et al. 1974; Yeung 1970). When dogs administered LD_{70} E. coli endotoxin were infused with 50% dextrose at rates sufficient to maintain blood glucose at control values, 100% of the animals lived (Hinshaw et al. 1974c). Administration of 50% glucose has been reported to elicit beneficial myocardial responses and elevation in cardiac output. The effects of hypertonic glucose in critically ill patients has been studied by Pindyck's group (1974) and they observed elevations in cardiac output and left ventricular stroke work. These observations, including the hypoglycemia of canine endotoxin shock, the survival benefits of infused glucose (Berk et al. 1970; Hinshaw et al. 1974c) in endotoxin shock, and recent reports of hypoglycemia in septic shock (Berk et al. 1970; Rackwitz et al. 1974; Yeung 1970) strongly suggest that elevated blood glucose concentrations should augment myocardial performance. Results from the present study fail to confirm this possibility since severe myocardial dysfunction occurred, although 50% glucose had been infused for about 2 hours in one series and arterial glucose concentrations were maintained constant in both series. A recent report documented myocardial failure after endotoxin injection at glucose concentrations between 5 and 125 mg%, while maintenance of glucose at control or higher values by infusion was without benefit to the myocardium (Hinshaw et al. 1976). These findings suggest that the reported beneficial effects of hypertonic glucose may be due to peripheral rather than direct cardiac action.

Although the normal heart derives most of its energy for contraction from free fatty acid (Bing 1965; Spitzer et al. 1974), the anaerobic

metabolism of glucose is the main source of energy for the ischemic myo-
cardium (Morgan et al. 1959; Neely and Morgan 1974; Stremple et al. 1976).
Morgan and co-workers (1959) have demonstrated in the isolated rat heart
that hypoxia induces a two-fold increase in glucose transport, whereas
insulin causes a three- to four-fold increase. The protective effects of
glucose and/or glycogen on the hypoxic heart, as determined by left
ventricular work (Hewitt et al. 1974), have been reported. Further,
Stremple and associates (1976) have demonstrated an increased myocardial
utilization of hypertonic glucose during hemorrhagic shock and suggested
that this form of shock is complicated by both hypoxia and ischemia.
Since maintenance of coronary arterial glucose concentration at approxim-
ately 100 mg% with 50% glucose in the present study did not prevent heart
failure, these findings suggest that neither hypoxia nor ischemia are
significant factors contributing to the myocardial dysfunction observed
in endotoxin shock.

Diabetic-like glucose tolerance responses have been observed in
septic shock patients (Gump et al. 1974). Increased tissue insulin
resistance has been observed in injured soldiers (Howard 1955) and rats
(Chaudry et al. 1974) subjected to hemorrhagic shock. The minimum amount
of insulin needed to correct the myocardial dysfunction by returning
LVEDP and power to control values was the amount infused in each study.
Insulin infusion rate averaged 6 U/min in the two series. Although plasma
insulin concentrations were assayed to be 30 and 43 μU/ml after endotoxin
administration, normally adequate concentrations to maintain function of
cardiac muscle, hearts still failed. These failures also occurred in
spite of maintaining blood glucose concentrations at a mean of 105 mg%.
The average absolute amount of infused insulin needed to correct myocardial

dysfunction was 150 units and when assayed this amount of insulin was 80,000 μU/ml, suggesting an insulin resistance of the myocardium in endotoxin shock.

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Table 1. Effects of insulin on myocardial performance and hemodynamics

following a 3.5-hr period of aortic hypotension and endotoxin[a]

Parameter	Control[b]	Postendotoxin (mean, 3.5 hr)		Postinsulin (mean, 45 min) Postendotoxin (mean, 4.5 hr)	
Mean aortic pressure, 50 mmHg					
LVEDP (mmHg)	3.6(0.3)	6.1(0.6)	(p<0.01)	3.9(0.4)	
Power (g·m/sec)	4.6(0.3)	4.3(0.3)	(p<0.01)	4.7(0.3)	
+dP/dt (mmHg/sec)	1357(88)	1286(85)		1536(124)	(p<0.05)
-dP/dt (mmHg/sec)	1482(132)	1221(153)	(p<0.05)	1757(160)	(p<0.02)
Heart rate (beats/min)	147(7)	130(4)	(p<0.05)	128(4)	(p<0.02)
Coronary flow (ml/min)	27(3)	31(2)		30(2)	
Glucose[c] (mg/100 ml)	123(7)	113(6)		109(7)	

[a]Data from 7 isolated canine heart preparations maintained at constant cardiac output and mean aortic pressures of 25-50 mmHg (performance evaluated at 50 mmHg). Ranges of insulin infused, 40-260; mean, 123 units. Statistical significance compared to control values. (Mean ±SE).

[b]LD_{100} E. coli endotoxin (3 mg/kg) injected immediately after control values were obtained.

[c]Maintained constant with 50% glucose infusion.

Table 2. Effects of insulin on arterial concentrations following a 3.5-hr period of aortic hypotension and endotoxin[a]

Parameter	Control[b]	Postendotoxin (mean, 3.5 hr)	Postinsulin (mean, 45 min) Postendotoxin (mean, 4.5 hr)
Mean aortic pressure, 50 mmHg			
Potassium (mEq/L)	3.2(0.1)	4.0(0.1) (p<0.001)	3.7(0.4)
Glucose[c] (mg/100 ml)	123(7)	113(6)	109(7)
Lactate (mg/100 ml)	17.6(4.4)	36.3(6.5) (p<0.02)	40.7(7.8) (p<0.05)
Insulin infused (units)	0	0	123(44)
Insulin assayed (µU/ml)	16(3)	30(11)	115,166(97,024)

[a]Data from 7 isolated canine heart preparations maintained at constant cardiac output and mean aortic pressures of 25-50 mmHg (evaluations made at 50 mmHg). Ranges of insulin infused, 40-260; mean, 123 units. Statistical significance compared to control values. (Mean±SE).

[b]LD$_{100}$ E. coli endotoxin (3 mg/kg) injected immediately after control values were obtained.

[c]Maintained constant with 50% glucose infusion.

Table 3. Effects of insulin on myocardial metabolism following a 3.5-hr period of aortic hypotension and endotoxin[a]

Parameter	Control[b]	Postendotoxin (mean, 3.5 hr)		Postinsulin (mean, 45 min) Postendotoxin (mean, 4.5 hr)	
Mean aortic pressure, 50 mmHg					
Lactate uptake (mg/min)	1.0(0.7)	2.0(0.3)		2.4(0.4)	($p < 0.02$)
O_2 uptake (ml/min)	3.0(0.2)	3.2(0.2)		2.9(0.1)	
CO_2 production (ml/min)	2.6(0.2)	3.1(0.2)	($p < 0.05$)	2.7(0.1)	
RQ (mg/min)	.87(.02)	.96(.02)	($p < 0.02$)	.91(.04)	
Glucose delivery (mg/min)	34(5)	35(4)		32(3)	

[a]Data from 7 isolated canine heart preparations maintained at constant cardiac output and mean aortic pressures of 25-50 mmHg (metabolism evaluated at 50 mmHg). Ranges of insulin infused, 40-260; mean, 123 units. Statistical significance compared to control values. (Mean±SE).

[b]LD_{100} E. coli endotoxin (3 mg/kg) injected immediately after control values were obtained.

Table 4. Effects of insulin on myocardial performance and hemodynamics following a 3.5-hr period of aortic hypotension and endotoxin[a]

Parameter	Control[b]		Postinsulin (mean, 65 min) Postendotoxin (mean, 5 hr)	
	100	150	100	150
Mean aortic pressures, 100 and 150 mmHg				
LVEDP (mmHg)	3.7(0.5)	6.4(0.9)	3.6(0.3)	6.1(1.0)
Power (g·m/sec)	9.5(0.6)	14.2(0.9)	9.4(0.6)	14.1(0.8)
+dP/dt (mmHg/sec)	2188(142)	3296(279)	2704(264) ($p<0.05$)	4202(300) ($p<0.01$)
-dP/dt (mmHg/sec)	2964(168)	3650(318)	2821(156)	3911(250)
Heart rate (beats/min)	153(8)	153(7)	139(8) ($p<0.01$)	141(10) ($p<0.05$)
Coronary flow (ml/min)	42(6)	69(9)	58(5)	107(11)

[a] Data from 7 isolated canine heart preparations maintained at constant cardiac output and mean aortic pressures of 25-50 mmHg (performance evaluated at 100 and 150 mmHg). Ranges of insulin infused, 40-260; mean, 123 units. Myocardial performance was not evaluated at 100 or 150 mmHg during the hypotensive period because raising aortic pressure was considered a therapy. Statistical significance compared to controls. (Mean±SE).

[b] LD_{100} E. coli endotoxin (3 mg/kg) injected immediately after control values were obtained.

Table 5. Effects of insulin on myocardial performance and hemodynamics following a 1.5-hr period of aortic hypotension 5-6 hrs after endotoxin[a]

Parameter	Postendotoxin (mean, 5 hr)[b]	Postinsulin (mean, 50 min) Postendotoxin (mean, 6 hr)	
Mean aortic pressure, 50 mmHg			
LVEDP (mmHg)	8.4(0.7)	5.4(0.5)	(p<0.005)
Power (g·m/sec)	5.0(0.4)	5.4(0.4)	(p<0.01)
+dP/dt (mmHg/sec)	1125(85)	1375(121)	(p<0.02)
-dP/dt (mmHg/sec)	1208(119)	1517(169)	(p<0.05)
Heart rate (beats/min)	149(9)	140(8)	(p<0.02)
Coronary flow (ml/min)	37(3)	51(15)	
Glucose[c] (mg/100 ml)	97(3)	101(9)	

[a]Data from 6 isolated canine heart preparations maintained at constant cardiac output and mean aortic pressures of 30-50 mmHg (performance evaluated at 50 mmHg). Ranges of insulin infused, 60-340; mean, 188 units. LD$_{90}$ E. coli endotoxin (2.5-3.0 mg/kg) injected into heart donor and support animal 5 hrs before first evaluation period and 3-4 hrs before isolating the left ventricle. Statistical significance compared to values at initial 50 mmHg. (Mean±SE).

[b]LVEDP was +13.6 mmHg 20 min after this evaluation period (50 mmHg).

[c]Maintained constant with 50% glucose infusion.

Table 6. Effects of insulin on arterial concentrations of potassium and lactate 5-6 hrs after endotoxin[a]

Parameter	Postendotoxin (mean, 5 hr)	Postinsulin (mean, 50 min) Postendotoxin (mean, 6 hr)
Mean aortic pressure, 50 mmHg		
Potassium (mEq/L)	3.9(0.2)	3.1(0.2) (p<0.001)
Glucose[b] (mg/100 ml)	97(3)	101(9)
Lactate (mg/100 ml)	28(3)	35(6)
Insulin infused (units)	0	188(56)
Insulin assayed (µU/ml)	43(10)	37,780(22,799)

[a]Data from 6 isolated canine heart preparations maintained at constant cardiac output and mean aortic pressure of 30-50 mmHg (evaluations made at 50 mmHg). Ranges of insulin infused, 60-340; mean, 188 units. LD$_{90}$ E. coli endotoxin (2.5-3.0 mg/kg) injected into heart donor and support animal 5 hrs before first evaluation period and 3-4 hrs before isolating the left ventricle. Statistical significance compared to values at initial 50 mmHg. (Mean±SE).

[b]Maintained constant with 50% glucose infusion.

Table 7. Effects of insulin on myocardial metabolism 5-6 hrs after endotoxin[a]

Parameter	Postendotoxin (mean, 5 hr)	Postinsulin (mean, 50 min) Postendotoxin (mean, 6 hr)
Mean aortic pressure, 50 mmHg		
Lactate uptake (mg/min)	1.5(0.8)	2.9(1.3)
O$_2$ uptake (ml/min)	3.4(0.3)	3.9(0.3)
CO$_2$ production (ml/min)	2.9(0.2)	3.6(0.2)
RQ (mg/min)	.87(.05)	.98(.05)
Glucose delivery (mg/min)	36(4)	48(9)

[a]Data from 6 isolated canine heart preparations maintained at constant cardiac output and mean aortic pressure of 30-50 mmHg (metabolism evaluated at 50 mmHg). Ranges of insulin infused, 60-340; mean, 188 units. LD$_{90}$ E. coli endotoxin (2.5-3.0 mg/kg) injected into heart donor and support animal 5 hrs before first evaluation period and 3-4 hrs before isolating the left ventricle. Statistical significance compared to values at initial 50 mmHg. (Mean±SE).

Table 8. Effects of insulin on myocardial performance and hemodynamics 5-6 hrs after endotoxin[a]

Parameter	Postendotoxin (mean, 5 hr)		Postinsulin (mean, 65 min) Postendotoxin (mean, 6.5 hr)	
	100	150[b]	100	150
Mean aortic pressures, 100 and 150 mmHg				
LVEDP (mmHg)	10.3(0.9)	17.2(5.6)	5.3(0.7)	8.8(1.2) (p<0.05)
Power (g.m/sec)	10.8(0.8)	16.3(1.3)	11.4(0.8)	17.0(1.2)
+dP/dt (mmHg/sec)	1829(140)	2874(241)	2412(166) (p<0.025)	3498(146) (p<0.02)
-dP/dt (mmHg/sec)	2090(170)	2900(417)	2438(176)	3229(203)
Heart rate (beats/min)	155(8)	156(9)	146(7)	151(7)
Coronary flow (ml/min)	71(7)	139(14)	78(12)	133(23)

[a]Data from 6 isolated canine heart preparations maintained at constant cardiac output and mean aortic pressure of 30-50 mmHg (performance evaluated at 100 and 150 mmHg). Ranges of insulin infused, 60-340; mean, 188 units. LD E. coli endotoxin (2.5-3.0 mg/kg) injected into heart donor and support animal 5 hrs before first evaluation period and 3-4 hrs before isolating the left ventricle. Statistical significance compared to initial 100 and 150 mmHg values, respectively. (Mean±SE).

[b]Total, 5 hearts; one failed to function at initial 150 mmHg.

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13. ABSTRACT

Recent data reported from this laboratory have documented myocardial dysfunction in canine endotoxin shock. The purpose of the present study was to determine the separate effects of insulin and glucose on the failing canine myocardium. Two groups of experiments were conducted on isolated working left ventricular preparations in which LD_{100} endotoxin was administered prior to, or following, isolation of the heart. Myocardial dysfunction occurred between 2 and 6 hours post-endotoxin, as evidenced by significantly increased left ventricular end diastolic pressure, depressed power and negative dP/dt, although blood glucose concentrations were maintained at control values. Insulin infusion, at mean rates of 6 units/minute administered via left atrial cannulation, reversed all signs of myocardial failure. During insulin infusion, heart rates decreased ($p < 0.02$) and myocardial lactate uptake increased ($p < 0.02$), while oxygen uptake and coronary blood flow were insignificantly altered. Findings indicate that the positive inotropic effects of insulin occur without additional oxygen requirements.

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